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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/576,724	05/23/2000	Vladka Curin-Serbec	201196/50 (80242/US)	3140

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EXAMINER	
WINKLER, ULRIKE	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 09/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/576,724	CURIN-SERBEC, VLADKA	
	Examiner	Art Unit	
	Ulrike Winkler	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,6,12-14,24-27 and 31-33* is/are pending in the application.

4a) Of the above claim(s) *24-27 and 31-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,6 and 12-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed March 8, 2004 in response to the Office Action of November 3, 2003 is acknowledged and has been entered. Claims 1-5, 12-14, 20 and 32-34 are pending and are currently being examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 112

The rejection of claims 1-5, 12, 13, 20 and 32-34 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specifically disclosed monoclonal antibody produced by the hybridoma CNCM- I-2476, does not reasonably provide enablement for other antibodies that are able to bind the prion specific protein structure while not binding the normal cellular form of the prion protein **is maintained** for reasons of record.

Applicants' argument is directed to the process of making the antibodies. This line of arguments is not convincing because the instant invention is limited to the composition, the antibody. Product-by-process claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps. M.P.E.P. Section 2113. In this instance the claims do not recite process steps yet applicants arguments are directed to the differences in the process of making the claimed antibodies an the cited art, Fishleigh et al. and O'Rourke. Applicants acknowledge that the prior art has attempted to make the instantly claimed antibodies, namely antibodies that exclusively bind the PrP^{Sc} form (the disease from) of the prion protein and not the cellular form of PrP^{C} under non-denaturing conditions. The Office cited the prior art precisely to

establish that the production of antibodies to a structural variant form is not predictable. Animals posses the normal cellular form of the prion protein (PrP^C) and for yet unexplained reasons at times this protein changes its from a primarily alpha helical conformation (PrP^C) to a primarily beta sheet conformation (PrP^{Sc}). This beta sheet conformation (PrP^{Sc}) is very stable and is the conformation that leads to agglutination of the fibrils and eventually leads to the formation of holes (spongiform) in the brain tissue. The problem arises is that both PrP^C and PrP^{Sc} have the identical linear amino acid sequence. The production of antibodies in an animal is hindered by the fact that the body normally expressed PrP^C on the cell surface and the body does not easily make antibodies against self-protein. The prior art has attempted to override the bodies immune protection against making antibodies to self protein by mixing fragments of the prion protein to various carrier molecules so that they are made to resemble foreign epitopes in order to elicit an antibody response (Fishleigh et al. and O'Rourke). This production method has been very unpredictable and oftentimes it has not resulted in success. An alternate method of antibody production is made through the use of recombinant animals Prnp 0/0 mice that doe not express cellular prion (PrP^C) on the surface of cells. In these animals the injection of prion protein PrP^C or PrP^{Sc} results in the production of antibodies, the problems with the resulting antibodies is that they often times recognize both forms of the protein PrP^C and PrP^{Sc}. Thus even the use of a knockout animal does not guarantee the production of an antibody that is specifically directed to the disease form vs. the cellular form.

In the instant specification the Applicants use Balb/c mice (these mice express the cellular form of the prion protein) and they inject the peptide attached to a carrier KLH into the animal (see examples). The animals were tested for the production of antibodies to the peptide

conjugate (peptide-KLH) and hybridomas were then made from these animals. Of all the hybridomas tested Applicants have found only a single CNCM- I-2476 hybridoma that exclusively binds PrP^{Sc}. Based on looking at Applicants procedure and comparing the procedure of Fishleigh et al. and O'Rourke there is not objective evidence in the instant specification that Applicants procedure is more successful and more predictable at producing antibodies that exclusively bind PrP^{Sc}. If this were the case the ordinary artisan would have expected more than a single hybridoma to meet the criteria of the claimed invention.

The antibodies of the prior art using the process disclosed in the prior art do not provide antibodies that have the specificity of the instantly claimed antibodies even though the prior art antibodies are capable of recognizing the same sequence. Fishleigh et al. (U.S. Pat. No. 5,773,572) and O'Rourke (U.S. Pat. No. 6,261,790 B1) teach that the production of antibodies that meet the limitation of binding the disease specific form while not binding the cellular form of the prion protein in a sample is not a trivial undertaking and is not predictable. Fishleigh et al. and O'Rourke immunize animals with peptides that the ordinary artisan would predict to have the essential 3-dimensional structure of SEQ ID NO: 1 or 2, yet the antibodies produced do not meet the requirement of binding the disease specific form while not binding the cellular form. Applicants have only provided a single antibody made by the disclosed method that meets the requirement of binding the disease specific form while not binding the cellular form. Given the difficulty in the art in producing an antibody that may meet this particular binding requirement, it appears that undue experimentation would be required to practice the claimed inventions with a reasonable expectation of success. Therefore, applicant is enabled only for the single disclosed antibody made from the CNCM- I-2476 hybridoma.

Claim Rejections - 35 USC § 102

The rejection of claims 1, 5, 12, 13 and 20 under 35 U.S.C. 102(b) as being anticipated by Prusiner et al. (U.S. Pat. No. 5,846,533) **is withdrawn** in view of Applicants amendments o the claims.

The rejection of claims 1, 2, 5, 12, 13, 32 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Korth et al. (Nature, 1997) **is maintained** for reasons of record.

Applicant's arguments are directed at the 15B3 antibody disclosed in the Korth et al. reference and that the antibody binds to a conformational epitope constituted by three non-contiguous amino acid sequences of recombinant bovine PrP. Applicant does acknowledge that the 15B3 antibody is capable of distinguishing between PrP^{C} and PrP^{Sc}. Applicant goes on to argue that the 15B3 antibody has a preference for PrP^{Sc} but does not bind exclusively to PrP^{Sc}. Applicants assertion that proteinase K must always be used is not correct. In figure 1c, mouse PrP^{Sc} was immunoprecipitate, only in the PrP^{Sc} homogenates was a positive band visualized. Here the samples were either not treated with proteinase K, or treated with proteinase K before or after the immunoprecipitation. The control brain which only possessed PrP^{C} did not precipitate any sample using the 15B3 antibody. Thus applicants assertion that the 15B3 antibody also detects PrP^{C} is not persuasive based on the reference. Applicants citation of the Aguzzi et al reference as showing that the 15B3 antibody is not exclusive for its binding to PrPSc is not persuasive because the reference does not explain what they mean by expectations. Furthermore the reference does indicate that it is difficult to make antibodies that are able to discriminate because the epitopes are not exclusive to one conformation vs. the other.

"Even if a reference discloses an inoperative device, it is prior art for all that it teaches." *Beckman Instruments v. LKB Produkter AB*, 892 F.2d 1547, 1551, 13 USPQ2d 1301, 1304 (Fed. Cir. 1989).

Korth et al. discloses the 15B3 antibody, which is able to recognize the disease specific form of the prion protein while not recognizing the cellular form (see figure 1). The antibody was screened against a peptide library and in this screen is able to individually bind 3 distinct peptides, this does not mean that the antibody is limited to only binding proteins that comprise the three peptides at the same time. The antibody is able to bind the epitope set out in SEQ ID NO:2 and the epitope of SEQ ID NO: 1 having at least one or more substitutions. Therefore, the instant invention is anticipated by Korth et al.

The rejection of claims 1, 2, 5, 12, 13, 32 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Korth et al. (EP 0 861 900 A1) **is maintained** for reasons of record.

Applicant's arguments are directed at the 15B3 antibody disclosed in the Korth et al. reference and that the antibody binds to a conformational epitope constituted by three non-contiguous amino acid sequences of recombinant bovine PrP. Applicant does acknowledge that the 15B3 antibody is capable of distinguishing between PrP^{C} and PrP^{Sc}. Applicant goes on to argue that the 15B3 antibody has a preference for PrP^{Sc} but does not bind exclusively to PrP^{Sc}. Applicants assertion that proteinase K must always be used is not correct. In figure 1c, mouse PrP^{Sc} was immunoprecipitate, only in the PrP^{Sc} homogenates was a positive band visualized. Here the samples were either not treated with proteinase K, or treated with proteinase K before or after the immunoprecipitation. The control brain which only possessed PrP^{C} did not

precipitate any sample using the 15B3 antibody. Thus applicants assertion that the 15B3 antibody also detects PrP^C is not persuasive based on the reference. Applicants citation of the Aguzzi et al reference as showing that the 15B3 antibody is not exclusive for its binding to PrPSc is not persuasive because the reference does not explain what they mean by expectations. Furthermore the reference does indicate that it is difficult to make antibodies that are able to discriminate because the epitopes are not exclusive to one conformation vs. the other.

"Even if a reference discloses an inoperative device, it is prior art for all that it teaches." *Beckman Instruments v. LKB Produkter AB*, 892 F.2d 1547, 1551, 13 USPQ2d 1301, 1304 (Fed. Cir. 1989).

Korth et al. discloses the 15B3 antibody, which is able to recognize the disease specific form of the prion protein while ot recognizing the cellular form. Figure 6b indicates that the antibody 15B3 recognizes only PrPSc but not PrPC. The antibody is able to bind the epitope set out in SEQ ID NO:2 and the epitope of SEQ ID NO: 1 having at least one or more substitutions. Therefore, the instant invention is anticipated by Korth et al.

New Rejection: Claims 1, 2, 5, 12, 13, 32 and 33 are rejected under 35 U.S.C. 102(e) as being anticipated by Korth et al. (US Pat. No. 6,765,088).

Korth et al. discloses the 15B3 antibody, which is able to recognize the disease specific form of the prion protein while ot recognizing the cellular form. Figure 6b indicates that the antibody 15B3 recognizes only PrPSc but not PrPC. The antibody is able to bind the epitope set out in SEQ ID NO:2 and the epitope of SEQ ID NO: 1 having at least one or more substitutions. Therefore, the instant invention is anticipated by Korth et al.

Allowable subject matter

Claims limited to the specific monoclonal antibody derived from the CNCM- I-2476 hybridoma cell line would be allowable.

Conclusion

Claims 6 and 14 would be allowable if rewritten in independent form.

Claims 1, 3, 5, 12, 13, 20 and 32 are rejected.

Papers related this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989). The Group 1600 Official Fax number is: (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 571-272-0902.

ULRIKE WINKLER, PH.D.
PRIMARY EXAMINER 9/16/05